PATENT SPECIFICATION 843,135

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Inventors:—SIEGFRIED GOTTFRIED and LILY BAXENDALE.

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COMPLETE SPECIFICATION.

Glycyrrhetinic Acid Salts.

We, BIOREX LABORATORIES LIMITED, a British Company, organised under the laws of Great Britain, of 47/51 Exmouth Street, Rosebery Avenue, London, E.C.1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention comprises improvements in and relating to pharmacological compounds, and more particlularly new derivatives of glycyrrhetinic acid.

Glycyrrhetinic acid is obtainable from liquorice root. In Specifications Nos. 798,655 and 799,415 we have described and claimed compositions containing glycyrrhetinic acid and having a pronounced effect in suppressing inflammation. The said compositions are suitable for topical application. Glycyrrhetinic acid being only sparingly soluble in water.

We have now found that the organic salts of glycyrrhetinic acid also have a good effect in suppressing inflammation, and yet are more soluble generally, especially in body fluids than glycyrrhetinic acid, and are, therefore, more suitable for systemic use than is glycyrrhetinic acid. It is to be understood that the new compounds are prepared from non-toxic bases which are compatible with mammals.

The new organic salts of glycyrrhetinic acid are prepared by methods in use or described in the literature for the conversion of organic acids to their salts with organic bases. Thus, they may be prepared by the interaction of the organic base with glycyrrhetinic acid, preferably in aqueous or organic media; in some cases an elevated temperature is useful in order to accelerate the salt formation.

These new compounds have a good effect in suppressing inflammation and may be used in compositions with known additives, such as with inert carriers, to form, for example, an ointment, powder, or emulsion, and may also be compounded with anti-causative agents, as is the case with glycyrrhetinic acid itself (e.g. as described in Specifications Nos. 798,655, 799,415 and 26332/57 (Serial No. 843,134)). Further the new compounds may be dissolved in suitable solvents, such as water, normal saline or oils, and so make compositions suitable for, for example oral, sub-cutaneous, intramammary, intra-muscular, intra-articular, intra-peritoneal and intravaneous use.

Medical, pharmacological, and veterinary tests and trials have been carried out with these new compounds on human beings, small and large animals, as well as pharmacological trials using rats, mice, guinea pigs, rabbits and cats. The new compounds have shown that the hereinafter-described derivatives are active in suppressing inflammation, for example pharmacological tests carried out as is more particularly described below:

These new compounds heal artificial lesions produced on the skin of rabbits, whether from an external cause, or from intradermal injections of irritant substances.

When applied locally, these new compounds cause rapid subsidence of any inflammation produced by the introduction of irritant substances into the eye of the rabbit.

When applied by systemic injection or by oral administration these new compounds depress the formation of granuloma tissue induced by subcutaneously-implanted cotton wool pellets in rats in the test described by Meier, R., Schuler, W., and Desaulles, P., Experientia, 1950, *6*, 469. These new derivatives depress the formation of inflammatory exudate and of the granulomatous membrane in the granuloma pouch test described by Selye, H., Britt. med. J., 1949, *2*, 1129.

When injected systemically into B.C.G.-infected guinea pigs, the new derivatives suppress the reaction to intra-dermally-injected tuberculin in the test described by Long, D. A., and Miles, A. A., Lancet, 1950, *1*, 492.

In addition, when injected parenterally or administered orally, the new derivatives have a mild depressant action in mice and potentiate the actions of central nervous system depressant drugs such as hexobarbitone.

The new derivatives have mild analgesic and antipyretic actions.

These new compounds are of value in combating inflammatory conditions of all types of denominations, such as inflammatory conditions of the skin, eye, ear, nose, mouth, dental cavities, genitals, rheumatic conditions, rectal conditions, inflammatory and ulcerative conditions of the digestive system, ulcerative colitis, allergic conditions, vaginitis, vulvitis, dysmenorrhoea, metritis, leukorrhoe, mastitis, and other inflammatory processes whether they be primary or of secondary cause, or the result of such cause.

These new compounds have also been found valuable in the treatment of severe emergencies, in which a "shock-like" state occurs, by virtue of their high solubility in water.

These new compounds have also been found of value when injected into inflammed joints and it was found that symptomatic relief was obtained.

In addition, these new compounds are of value in a number of illnesses where a mild sedative, analgesic, or antipyretic may be indicated.

The glycyrrhetinic acid derivatives according to the present invention inhibit steroids and their metabolism, such as the usual hormonal secretions of glands, by reduction of glandular activity. They are useful in the treatment of anogenital diseases, such as vulvitis, vaginitis, ulcerations of the vaginal basin and cervix of the uterus, either alone or in association with leucorrhoea, menstrual disfunctions, ano-genital pruritis, and in the treatment of diseases, such as carcinomas, in which the inhibition of steroids or the reduction of hormonal glandular secretion is of therapeutic value, as well as inflammatory and ulcerative conditions of the digestive system.

The new compounds have a potentiating effect demonstrating synergism with antibiotic drugs, (such as Neomycin), keratoplastic drugs, (such as Coal Tar), keratolytic drugs, (such as Salicyclic Acid), analgesics, antiseptics, bateriocides, chemotherapeutics, bacteriostatics, anti-histaminics, sedatives, fungicides, insecticides, corticosteroids and xanthoglabrol.

Synergism has also been demonstrated in conjunction with corticosteroids, such others as hydrocortisone, prednisone and prednisolone, in the replacement therapy of adrenolectomised patients, as well as in Addision's disease, disseminated lupus erythematosus and acute bronchial asthma.

As has already been indicated, these new derivatives can be incorporated in various therapeuric forms, such as, ointments, solutions, injections, emulsions, suspensions, pastes, cones, cerates, paints, powders, and implants, all in conjunction with suitable carriers.

The following examples are given for the purpose of illustrating the invention:—

EXAMPLE 1.

Piperazine salt of glycyrrhetinic acid.

2.0 grams of piperazine hexahydrate were dissolved in 200 cc. of boiling water. 9.0 grams of glycyrrhetinic acid were added, as an aqueous paste, and then 200 cc. of rectified spirit. On boiling on a water bath, practically all the acid dissolved, and the suspension was filtered and the filtrate evaporated on the boiling water bath. Removal of water was completed by vacuum-drying over solid potassium hydroxide, and the solid piperazine salt of glycyrrhetinic acid obtained was then readily ground to a fine powder. This salt is more soluble in water than is glycyrrhetinic acid.

EXAMPLE 2.

N-methyl glucamine salt of glycyrrhetinic acid.

A solution of 8 grams of N-methyl-glucamine in 50 cc. of water was added to 19 grams of glycyrrhetinic acid, previously ground to a paste with 100 cc. of water. After warming to about 50° C. and shaking for a few minutes, the suspension was filtered and the filtrate evaporated on a water bath. The residue, which was the N-methyl-glucamine salt of glycyrrhetinic acid, was further freed from water by drying in a vacuum over concentrated sulphuric acid. The salt is very readily soluble in water, and is a white powder.

The triethanolamine salt and salts of other organic bases may be prepared in a similar manner.

EXAMPLE 3.

An ointment was prepared by dissolving 2% by weight of the piperazine salt of glycyrrhetinic acid and by 5% by weight of neomycin sulphate in a "Vaseline" (Registered Trade Mark) base. The base can also be made from 8% by weight of non-ionic emulsifying wax B.P.C. and 16% by weight of liquid paraffin in water.

EXAMPLE 4.

Ointments were prepared as described in Example 3 in which the neomycin sulphate was replaced by an equal amount of centrimide.

EXAMPLE 5.

An emulsion was prepared by dissolving 0.5% by weight of the N-methylglucamine salt of glycyrrhetinic acid, 0.5% by weight of hexachlorophene, 5% by weight of "Lanbritol" (Registered Trade Mark), 10% by weight of glycerol and 20% by weight of polyethylene glycol in water.

EXAMPLE 6.

A lotion was prepared by dissolving 1% by weight of the piperazine salt of glycyrrhetinic acid, 0.5 by weight of hydrocortisone alcohol, 0.5% by weight of coal tar fractions and 10% by weight of polyethylene glycol (molecular weight 600) in water. This example illustrates the replacement of hydrocortisone in a known preparation by a glycyrrhetinic acid derivative to give a preparation with an enhanced anti-inflammatory effect.

EXAMPLE 7.

A suppository was prepared by dispersing 1% by weight of the triethanolamine salt of glycyrrhetinic acid, 2% by weight of benzocaine and 5% by weight of 2:4- or 4:4-(diacetoxydiphenylmethyl) pyridine in a suppository base (British Pharamaceutical Codex).

EXAMPLE 8.

An injection was prepared containing 0.25 g. of the N-methylglucamine salt of glycyrrhetinic acid 0.048 g. methyl *p*-hydroxybenzoate, 0.08 g. "Tween" (Registered Trade Mark), which is a wetting agent and 0.1 g. "Edipas" (Registered Trade Mark), which is an edible cellulose derivative, in normal saline to make 20 ml.

Further ointments, emulsions, lotions, suppositories, tablets, injections and pessaries were prepared in a manner similar to those given in Examples 3—8 in which the glycyrrhetinic acid derivative was the sole active ingredient present.

WHAT WE CLAIM IS:—

1. Salts of glycyrrhetinic acid with organic bases.
2. Piperazine salt of glycyrrhetinic acid.
3. N-methylgluamine salt of glycyrrhetinic acid.
4. Triethanolamine salt of glycyrrhetinic acid.
5. Process for the production of organic salts of glycyrrhetinic acid, wherein the derivatives are prepared from glycyrrhetinic acid by methods known *per se* for the conversion of organic acids to their salts with organic bases.
6. Process for the production of organic salts of glycyrrhetinic acid, substantially as hereinbefore described and with reference to either of Examples 1 and 2.
7. Organic salts of glycyrrhetinic acid, whenever prepared by the process according to Claim 5 or 6.
8. Pharmaceutical and therapeutic compositions containing as active ingredient one or more glycyrrhetinic acid derivatives according to any of Claims 1—4 and 7, alone or in admixture with one or more antibiotics, keratoplastics, keratolytics, analgesics, bacteriocides, chematherapeutics, bacteriostatics, corticosteroids, xanthoglabrol, anti-histaminics, sedatives, fungicides and/or insecticides, and an inert pharmaceutical carrier.
9. Pharmaceutical and therapeutic compositions substantially as hereinbefore described wth reference to any of Examples 3—8.

CARPMAELS & RANSFORD,
Agents for Applicants,
24 Southampton Buildings,
Chancery Lane, London, W.C.2.

PROVISIONAL SPECIFICATION.

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ing inflammation. The said compositions are suitable for topical application, glycyrrhe, tinic acid being only sparingly soluble in water.

We have now found certain derivatives of glycyrrhetinic acid, which also have a good effect in suppressing inflammation, and yet are more soluble generally, especially in body fluids, than glycyrrhetinic acid, and are therefore, more suitable for systematic use than in glycyrrhetinic acid.

According to the invention, there are provided, as new compounds, organic salts of glycyrrhetinic acid. These new compounds have a good effect in suppressing inflammation and may be used in compositions with known additives, e.g. with inert carriers to form, e.g. an ointment, powder, or emulsion and also may be compounded with anti-causative agents, as is the case with glycyrrhetinic acid itself, e.g. as described in Specification Nos. 8183/56 and 8184/56 (Serial Nos. 798,665 and 799,415). Further the new compounds may be dissolved in suitable solvents, oral, e.g. water, normal saline, etc., and so make compositions suitable for e.g., sub-cutaneous, intra-muscular, intra-articular, intra-peritoneal and intra-venous use.

The following examples are given for the purpose of illustrating the invention, showing examples of new salts with organic bases.

For instance, new salts of glycyrrhetinic acid not described hitherto have been prepared.

EXAMPLE 1.

Piperazine salt of glycyrrhetinic acid.

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CARPMAELS & RANSFORD,
Agents for Applicants,
24 Southampton Buildings,
Chancery Lane, London, W.C.2.

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